EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

DYNAMAC CORPORATION
PROJECT NO. HET K-002372-22

SUBCHRONIC STUDY OF 2,4-D IN RATS

PATHOLOGY REPORT

Submitted to:

Dynamac Corporation
Rockville, MD 20852

January 16, 1989

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PATHOLOGY SUMMARY

DYNAMAC CORPORATION
PROJECT NO. HET K-002372-22

SUBCHRONIC STUDY OF 2,4-D IN RATS

PATHOLOGY SUMMARY

Microscopic evaluation of kidneys from 50 male and 50 female Fischer 344 rats was performed. These rats were on a 13-week study to evaluate the toxicological potential of technical grade 2,4-dichlorophenoxyacetic acid (2,4-D) herbicide. Following is the experimental design for this study:

Group No.	No. of Animals* Male	Female	Dietary Level mg/kg/day
1	15	15	0
2	15	15	15
3	15	15	60
4	15	15	100
5	15	15	150

*Histologic evaluation was performed on only 10 rats per sex at each dose group.

The microscopic changes for each kidney evaluated are presented in the Histopathology Incidence Tables. All lesions are summarized by sex and treatment group and presented in the Summary Incidence Tables.

RESULTS

Compound-related histomorphologic alterations were noted in the kidneys of both male and female rats in a dose-related manner. These lesions occurred in the outer stripe of the outer medulla, occasionally extending as medullary rays into the cortex proper. These lesions consisted of an increased number of cells in various tubules arranged more or less at regular intervals around the perimeter of this area. The term multifocal tubular cell hyperplasia was used for this change. In addition, a basophilic tint was present in the cytoplasm of the tubules in this area. Lesions occurred more frequently and were more severe in male rats than in female rats.

In the treated male rats, both of these alterations were present in nearly all of the animals examined; however, there was a definite and dramatic decrease in severity with decreasing dose, particularly in female rats receiving 15 mg/kg/day. In high dose males (150 mg/kg/day), multifocal tubular cell hyperplasia was graded moderate in eight rats and slight in two; tubular basophilia was graded moderate in three rats and slight in six. In males receiving 100 mg/kg/day, multifocal tubular cell hyperplasia was graded moderate in three rats and slight in seven; tubular basophilia was slight in four rats and minimal in six. In males receiving 60 mg/kg/day, multifocal tubular cell hyperplasia was slight in five rats and minimal in the other five; tubular basophilia was slight in two and minimal in seven. In the low

dose group (15 mg/kg/day), tubular cell hyperplasia was minimal in all but one rat and tubular basophilia was minimal in all 10.

In female rats, multifocal tubular cell hyperplasia was present in nearly all of the rats receiving 60, 100, and 150 mg/kg/day. Tubular basophilia was noted in nearly all of the treated rats. A definite dose relationship was evident, similar to that noted in the male rats. In the high dose females (150 mg/kg/day), multifocal tubular cell hyperplasia was graded slight in seven rats and minimal in three; tubular basophilia was slight in five rats and minimal in five. In females receiving 100 mg/kg/day, multifocal tubular cell hyperplasia and tubular basophilia were graded minimal in eight rats and slight in one. In females receiving 60 mg/kg/day, multifocal tubular cell hyperplasia was graded minimal in seven rats and slight in one; tubular basophilia was minimal in all 10. In low dose female rats (15 mg/kg/day), minimal tubular cell hyperplasia was noted in only one rat and minimal tubular basophilia was noted in seven.

It should be noted that in rats in which basophilia was noted to be minimal, variation in staining procedures and conditions may have been a factor. In rats in which tubular cell hyperplasia was graded minimal, only a few tubules in the affected area were diagnosed as having increases in cell number. In some cases, only two or three tubules were noted to be affected on the sections of kidneys examined.

The incidence of pelvic mineralization was also increased in treated rats. This lesion was noted in seven of 10 high dose males (150

mg/kg/day), one male receiving 100 mg/kg/day, three high dose females (150 mg/kg/day), five females receiving 100 mg/kg/day, and three females receiving 60 mg/kg/day. This lesion was not diagnosed in any of the control rats, low dose rats (15 mg/kg/day) or males receiving 60 mg/kg/day. There was no increase in the incidence of tubular mineralization, a lesion seen more frequently in female rats.

Spontaneous disease lesions and incidental findings were, for the most part, typical of the early lesions of chronic nephropathy occurring in aging rats. These lesions included interstitial nephritis, casts, interstitial fibrosis, and regenerative tubular epithelium. An early mesenchymal tumor was diagnosed in one high dose female and consisted of strands of embryonic-appearing mesenchyme proliferating between existing tubules and forming a space-occupying area. It should be noted that renal mesenchymal tumor tends to be a tumor of the young rats with rats over four months being resistant to its formation. Other lesions occurring infrequently were pelvic dilatation, tubular concretions, tubular pigment, and tubular vacuolization.

CONCLUSIONS

Histomorphologic alterations attributable to dietary administration of 2,4-D to Fischer 344 rats were present in the kidneys of rats receiving 15, 60, 100, and 150 mg/kg/day. These lesions occurred in the outer stripe area of the outer medulla and consisted of multifocal tubular cell hyperplasia and tubular basophilia. Lesions were more

severe and more frequent in males than in females. Lesions occurred in a dose-related manner. In females at the lowest dose, only minimal tubular basophilia was seen with minimal tubular cell hyperplasia occurring in only one rat. Pelvic mineralization was diagnosed only in treated rats and was present in the majority of the high dose males examined, in a single male receiving 100 mg/kg/day and in three to five females in the 60, 100, and 150 mg/kg/day groups.

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January 16, 1989

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EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE FINAL CERTIFICATION

Client Name Dynamac Corporation

EPL Project Coordinator Dr. William M. Busey

Client Study HET K-002372-22

EPL Pathologist Dr. Deborah A. Banas

Species Rat

EPL Project Number 252-018

Study Title Subchronic Study of 2,4-D in Rats

Test Article 2,4-D Technical Grade

The following phases of this study (marked by "X") were inspected by Experimental Pathology Laboratories Quality Assurance Unit. The dates of the inspections performed are as indicated below. All findings were reported to the EPL Project Coordinator and to Management.

(X)	Part	Date
X	1 of 6 - Project Sheet	9/20/88
___	2 of 6 - Master IAWS	N/A
___	3 of 6 - Histology Setup	N/A
___	4 of 6 - Histology Completion	N/A
X	5 of 6 - Rough Draft Report	1/12/89
X	6 of 6 - Final Report	1/16/89
___	Other -	N/A
Date of last quarterly inspection		9/88

This study is certified to have been performed in compliance with Good Laboratory Practices.

Quality Assurance Helen A Cook Date 1·16·89

Form No. 45 (Revised 2/5/88)

SUMMARY INCIDENCE TABLES

SUMMARY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Male Rat

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5	
KIDNEY (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Mesenchymal Tumor						
Cast(s)	7	8	5	1	2	
Interstitial Fibrosis	4	1	2	3	7	
Interstitial Nephritis	9	9	7	6	5	
Pelvic Dilatation, Unilateral				1		
Pelvic Mineralization				1	7	
Regenerative Tubular						
Epithelium	10	9	9	4	7	
Tubular Basophilia		10	9	10	9	
Tubular Cell Hyperplasia,						
Multifocal		10	10	10	10	
Tubular Concretion	4	2	5	3	3	
Tubular Mineralization	1	1	2	2		
Tubular Pigment				1		
Tubular Vacuolization	2	4	1	1	7	

SUMMARY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Female Rat

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5	
KIDNEY (NO. EXAMINED)	(10)	(10)	(10)	(10)	(10)	
Mesenchymal Tumor					1	
Cast(s)	3		1			
Interstitial Fibrosis	1					
Interstitial Nephritis	5	4	1	1	4	
Pelvic Dilatation, Unilateral						
Pelvic Mineralization			3	5	3	
Regenerative Tubular						
Epithelium	7	6	3	2	2	
Tubular Basophilia		7	10	9	10	
Tubular Cell Hyperplasia,						
Multifocal		1	8	9	10	
Tubular Concretion	1	2			1	
Tubular Mineralization	8	3	2	4	4	
Tubular Pigment			1	1		
Tubular Vacuolization						

HISTOPATHOLOGY INCIDENCE TABLES

DYNAMAC CORPORATION
PROJECT NO. HET K-002372-22

SUBCHRONIC STUDY OF 2,4-D IN RATS

GROUP NO.	NO. OF ANIMALS* MALE	FEMALE	DIETARY LEVEL MG/KG/DAY
1	15	15	0
2	15	15	15
3	15	15	60
4	15	15	100
5	15	15	150

*Histologic evaluation was performed on only 10 rats per sex at each dose group.

HISTOPATHOLOGY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Male Rat
Scheduled Sacrifices

GROUP 1

ANIMAL	78-448	78-488	78-489	78-489	78-489	78-489	78-489	78-489	78-489	78-489
KIDNEY										
Mesenchymal Tumor										
Cast(s)	1	1		1	1	1	1		1	
Interstitial Fibrosis			1			1	1		1	
Interstitial Nephritis	1	1		1	1	1	1	1	1	1
Pelvic Dilatation, Unilateral										
Pelvic Mineralization										
Regenerative Tubular										
Epithelium	2	1	1	1	2	2	1	2	2	1
Tubular Basophilia										
Tubular Cell Hyperplasia,										
Multifocal										
Tubular Concretion		1					1		1	1
Tubular Mineralization									1	
Tubular Pigment										
Tubular Vacuolization				2		1				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=slight/mild 3=moderate 4=moderately severe 5=severe/high
P=Present B=Benign M=Malignant
u=moribund sac./death

HISTOPATHOLOGY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Male Rat
Scheduled Sacrifices

GROUP 2

ANIMAL	78-449003	78-449004	78-449005	78-449006	78-449007	78-449008	78-449009	78-449010	78-449011	78-449012
KIDNEY										
Mesenchymal Tumor										
Cast(s)	1	1	1	1	1			1	1	1
Interstitial Fibrosis				1						
Interstitial Nephritis	1	1	1	1	1		1	1	1	1
Pelvic Dilatation, Unilateral										
Pelvic Mineralization										
Regenerative Tubular										
Epithelium	1	1	1	1	1	1	1	1		1
Tubular Basophilia	1	1	1	1	1	1	1	1	1	1
Tubular Cell Hyperplasia,										
Multifocal	1	1	1	2	1	1	1	1	1	1
Tubular Concretion							1			1
Tubular Mineralization	1									
Tubular Pigment										
Tubular Vacuolization	1		1	1				1		

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HISTOPATHOLOGY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Male Rat
Scheduled Sacrifices

GROUP 3

ANIMAL	78-4918	78-4919	78-4920	78-4921	78-4922	78-4923	78-4924	78-4925	78-4926	78-4927
KIDNEY										
Mesenchymal Tumor										
Cast(s)	1	1					1		1	1
Interstitial Fibrosis							1			1
Interstitial Nephritis	1	1		1	1	1		1	1	
Pelvic Dilatation, Unilateral										
Pelvic Mineralization										
Regenerative Tubular										
Epithelium	2	1		1	1	1	1	2	1	1
Tubular Basophilia	1	1		1	1	2	1	1	2	1
Tubular Cell Hyperplasia,										
Multifocal	1	2	1	1	2	2	1	2	2	1
Tubular Concretion		1	1	1				1		1
Tubular Mineralization				1			1			
Tubular Pigment										
Tubular Vacuolization	1									

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HISTOPATHOLOGY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Male Rat
Scheduled Sacrifices

GROUP 4

ANIMAL	78-4933	78-4934	78-4935	78-4936	78-4937	78-4938	78-4939	78-4940	78-4941	78-4942
KIDNEY										
Mesenchymal Tumor										
Cast(s)							1			
Interstitial Fibrosis	1		1					1		
Interstitial Nephritis	1		1	2		1	1		1	
Pelvic Dilatation, Unilateral			2							
Pelvic Mineralization						2				
Regenerative Tubular										
Epithelium	1	1	1							1
Tubular Basophilia	2	2	1	2	2	1	1	1	1	1
Tubular Cell Hyperplasia,										
Multifocal	2	2	2	2	3	2	2	3	2	3
Tubular Concretion	1					1		1		
Tubular Mineralization	1								1	
Tubular Pigment									2	
Tubular Vacuolization		1								

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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HISTOPATHOLOGY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Male Rat
Scheduled Sacrifices

GROUP 5

ANIMAL	78-449548	78-449549	78-449550	78-449551	78-449552	78-449553	78-449554	78-449555	78-449556	78-449557
KIDNEY										
Mesenchymal Tumor										
Cast(s)			1		1					
Interstitial Fibrosis	1	1	1	1	1	1	1			
Interstitial Nephritis		1		1	1	1	1			
Pelvic Dilatation, Unilateral										
Pelvic Mineralization			1	2	1		2	2	2	2
Regenerative Tubular										
Epithelium		1	1	1	1	1	1		1	
Tubular Basophilia	2	2	2	2	3	2	3	3		2
Tubular Cell Hyperplasia,										
Multifocal	3	3	2	3	3	3	3	3	2	3
Tubular Concretion	1	1								1
Tubular Mineralization										
Tubular Pigment										
Tubular Vacuolization	2		1	1	1	1	1	1		

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DYNAMAC CORPORATION
PROJECT NO. HET K-002372-22

SUBCHRONIC STUDY OF 2,4-D IN RATS

GROUP NO.	NO. OF ANIMALS* MALE	FEMALE	DIETARY LEVEL MG/KG/DAY
1	15	15	0
2	15	15	15
3	15	15	60
4	15	15	100
5	15	15	150

*Histologic evaluation was performed on only 10 rats per sex at each dose group.

HISTOPATHOLOGY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Female Rat
Scheduled Sacrifices

GROUP 1

ANIMAL	78-4963	78-4964	78-4965	78-4966	78-4967	78-4968	78-4969	78-4970	78-4971	78-4972
KIDNEY										
Mesenchymal Tumor										
Cast(s)	1					1		1		
Interstitial Fibrosis							1			
Interstitial Nephritis	1	1				1	1		1	
Pelvic Dilatation, Unilateral										
Pelvic Mineralization										
Regenerative Tubular Epithelium	1		1		1	1	1	1		1
Tubular Basophilia										
Tubular Cell Hyperplasia, Multifocal										
Tubular Concretion								1		
Tubular Mineralization	2	1	1	1	1		1		2	1
Tubular Pigment										
Tubular Vacuolization										

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u=moribund sac./death

HISTOPATHOLOGY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Female Rat
Scheduled Sacrifices

GROUP 2

	ANIMAL																			
	78-4978	78-4979	78-4980	78-4981	78-4982	78-4983	78-4984	78-4985	78-4986	78-4987										
KIDNEY																				
Mesenchymal Tumor																				
Cast(s)																				
Interstitial Fibrosis																				
Interstitial Nephritis						1		1	1	1										
Pelvic Dilatation, Unilateral																				
Pelvic Mineralization																				
Regenerative Tubular																				
Epithelium	1	1			1		1		1	1										
Tubular Basophilia		1	1		1	1	1	1	1											
Tubular Cell Hyperplasia,																				
Multifocal								1												
Tubular Concretion						1	1													
Tubular Mineralization		1		1			1													
Tubular Pigment																				
Tubular Vacuolization																				

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HISTOPATHOLOGY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Female Rat
Scheduled Sacrifices

GROUP 3

ANIMAL	78-4993	78-4994	78-4995	78-4996	78-4997	78-4998	78-4999	78-5000	78-5001	78-5002
KIDNEY										
Mesenchymal Tumor										
Cast(s)										1
Interstitial Fibrosis										
Interstitial Nephritis	1									
Pelvic Dilatation, Unilateral										
Pelvic Mineralization				2		1	1			
Regenerative Tubular										
Epithelium					1	1				1
Tubular Basophilia	1	1	1	1	1	1	1	1	1	1
Tubular Cell Hyperplasia,										
Multifocal	1			1	1	1	1	2	1	1
Tubular Concretion										
Tubular Mineralization					1	1				
Tubular Pigment	1									
Tubular Vacuolization										

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HISTOPATHOLOGY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Female Rat
Scheduled Sacrifices

GROUP 4

ANIMAL	78-50008	78-50009	78-50010	78-50011	78-50012	78-50013	78-50014	78-50015	78-50016	78-50017
KIDNEY			X							
Mesenchymal Tumor										
Cast(s)										
Interstitial Fibrosis										
Interstitial Nephritis				1						
Pelvic Dilatation, Unilateral										
Pelvic Mineralization		2		1		1	1			1
Regenerative Tubular										
Epithelium		1		1						
Tubular Basophilia	1	1		1	1	1	1	2	1	1
Tubular Cell Hyperplasia,										
Multifocal	1	1		1	1	2	1	1	1	1
Tubular Concretion										
Tubular Mineralization				1			1		1	1
Tubular Pigment									1	
Tubular Vacuolization										

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HISTOPATHOLOGY INCIDENCE TABLE

HET K-002372-22
Terminal Sacrifice
Female Rat
Scheduled Sacrifices

	GROUP 5																			
ANIMAL	78-5023	78-5024	78-5025	78-5026	78-5027	78-5028	78-5029	78-5030	78-5031	78-5032										
KIDNEY																				
Mesenchymal Tumor					P															
Cast(s)																				
Interstitial Fibrosis																				
Interstitial Nephritis		1		1	1					1										
Pelvic Dilatation, Unilateral																				
Pelvic Mineralization		1		1	1															
Regenerative Tubular																				
Epithelium		2			1															
Tubular Basophilia	2	1	2	1	1	1	2	1	2	2										
Tubular Cell Hyperplasia,																				
Multifocal	1	1	2	2	2	2	2	2	1	2										
Tubular Concretion									1											
Tubular Mineralization				1		1	1			1										
Tubular Pigment																				
Tubular Vacuolization																				

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